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The War on Cancer: Good News, Glum Faces

Researchers are heartened by positive trials of several new drugs, but the long-sought cure remains as remote as ever

The news from the world's largest meeting of cancer specialists is the best that it has been in years. And yet the mood of attending oncologists is subdued. As promising as the new generation of cancer medicines are, there is still no cure for one of humanity's most feared killers (see BW Online, 6/03/03, "The Best Offense Against Cancer").

After two years of setbacks, two experimental and controversial drugs -- Genentech's (DNA) Avastin and ImClone Systems' (IMCLE) Erbitux -- showed strong efficacy against the worst stages of colon cancer, the No. 2 cancer killer (see BW Online, 5/29/03, "Cancer Drugs: At Last, a Tonic for Biotech"). There was also good data on a number of the other new, so-called targeted cancer drugs, as well as improvements in the use of existing forms of chemotherapy that promise a kinder, gentler, more effective standard of care for a number of cancers. "This meeting is one for the record books. We're seeing very exciting progress," says one of the world's leading colon-cancer specialists, Dr. Leonard Saltz of Memorial Sloan-Kettering Cancer Center in New York "But is it good enough? No. It stinks."

VINDICATED. Granted, scientists see the latest drugs as a significant step forward after 30 years of difficult research. But the message clinicians will take home from the four-day meeting of the American Society of Clinical Oncology (ASCO) is that they may be able to contain advanced cancer for a matter of months or, for a lucky few, even years. But that's cold comfort for the 556,500 patients who will die of cancer in the U.S. this year. Approximately 1.3 million new cancer cases will be diagnosed in 2003, oncologists estimate. Consequently, scientists at the important ASCO meeting are quick to follow up public statements of enthusiasm about new treatments with expectation-dampening qualifiers. They've learned their lesson after the many very public ups and downs of Avastin and Erbitux.

Avastin was written off by many specialists and industry analysts after Genentech reported disappointing data on a trial of the drug in late-stage breast-cancer patients at last year's ASCO meeting. Erbitux was the centerpiece of an insider-trading scandal at ImClone after the Food & Drug Administration famously rejected the drug's application filing in 2001 because of questions about the results of the clinical trials.

CHEMO BOOSTER. Both drugs have now been vindicated. Avastin in particular may win over its many skeptics who question its approach to fighting cancer: cutting off the blood supply to the tumor. This area of drug development, called antiangiogenesis, was heralded on the front page of *The New York Times* several years ago as a likely cure for cancer after promising results in mice.

Yet since then, the field has been littered with failures. Most of the dozens of antiangiogenic drugs in clinical trials are considered at best to be adjuncts to chemotherapy, used to boost its effectiveness. But that's not necessarily a bad thing. In the data presented at ASCO, Avastin combined with standard chemotherapy was able to extend the lives of advanced-stage colon cancer patients by 4.9 months -- a significant achievement in patients that sick.

The Phase 3 trial involved 800 patients, half of whom randomly received the standard treatment for colon cancer -- a three-drug chemotherapy cocktail -- and half received the cocktail plus Avastin. Those on Avastin survived a median of 20.3 months, vs. 15.6 months on the standard treatment alone. In addition, the Avastin combination shrank tumors by at least half in 45% of patients, vs. 35% of patients who received just chemotherapy.

SIMILAR RESULTS. An additional five months of life may not seem like much, but in world of cancer research this is a very big deal. Although the goal of most of the new targeted therapies -- which aim only at tumor cells and carry minimal side effects -- has been to shrink tumors, few if any have demonstrated they can actually help patients live longer. Neither Novartis' Gleevec nor AstraZeneca's Iressa -- both targeted therapies approved with much fanfare in the last two years -- has proved a survival benefit. They were able to shrink the size of the tumor only, which doctors hope will translate into longer life.

Besides, notes Dr. Mace Rothenberg, a colon-cancer specialist with Vanderbilt-Ingram Cancer Center in Nashville, those five months represent a 30% improvement for patients dying of cancer -- and could well be very important to someone who has been told they have only a few months to live. "We're happy to take whatever we can get," says Rothenberg. "The longer they live, the more options these patients may have."

One other option may be Erbitux, ImClone's troubled drug. ImClone and U.S. development partner Bristol-Myers (BMY) have been plugging along with new clinical trials after the FDA rejected the ones submitted in an approval filing in December, 2001. Merck KgaA (no relation to the U.S. Merck), which holds rights to the drug in Europe, has continued on with its own trials of the drugs.

Those results, presented June 1 at ASCO, almost exactly matched the rejected ImClone results. Merck researchers said the drug combined with chemotherapy shrank tumors by 50% or more in 22.9% of patients with advanced-stage colon cancer, while 10.8% of patients who received Erbitux alone had tumor shrinkage. The ImClone data reported in 2001 showed tumor shrinkage in 22.5% of patients when used in combination. When used as a single agent, 10.9% of patients had tumor shrinkage.

FDA EXCEPTION? The Merck trial involved 329 patients, and doctors familiar with the study say it was far more rigorously designed than the earlier ImClone trial. "This agent is active. Some of the responses were very impressive," says Dr. David Cunningham of the Royal Marsden Hospital in England and lead investigator on the Merck trial. "As clinicians we've felt a strong sense of frustration about this valuable agent. We would like to see it in the clinic as soon as possible."

How quickly that might happen is open to question, however. Merck plans to file for approval in Europe this summer and says approval could come early next year. ImClone and Bristol Myers issued a statement saying they would also discuss with the FDA the possibility of using the European results in a U.S. reapplication. Industry analysts caution that the FDA rarely accepts European trial results, but there may be pressure from clinicians to moderate that stance given that there are so few treatments available for advanced colon cancer.

Meanwhile, Sloan-Kettering's Salz says trials are now being planned that would test Avastin and Erbitux together against colon cancer. "None of these drugs are the solution, but we're very interested in seeing what they can do together," he says. Still, the elusiveness of a cure can throw a pall even over significant advances.

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